

Remarks

Reconsideration of the Application is respectfully requested. Applicant respectfully requests entry of this amendment after final because the amendment to the claims places the claims in better form for allowance.

Upon entry of the foregoing amendment, claims 1-4, 6, 7, and 24-30 are pending in the application, with claim 1 being the independent claim. New claims 24-30 are sought to be added. Support for the amendments to the claims may be found throughout the specification as originally filed, either inherently or explicitly. Specifically, support for the amendment to claim 1 can be found in the specification at page 11, lines 16-20 and page 13, lines 10-19. Support for the addition of claims 24-30 can be found at page 11, lines 16-20. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicant respectfully requests that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Rejections under 35 U.S.C. § 112

The Examiner has maintained the rejection of claims 1-4, 6 and 7 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to use the invention. Office Action at page 2. Specifically, the Examiner states that "the rejection is on the grounds that the Applicant has not demonstrated that such products would be

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useful as vaccines against an infectious disease." Office Action at page 3. Applicant respectfully traverses this rejection.

T-Cell Receptor Mimic from Receptor Logic

Applicant submits that the enclosed product information from Receptor Logic demonstrates that the gene products identified by the claimed method are useful as vaccine candidates. Receptor Logic has developed an integrated diagnostic and therapeutic approach for the design of anti-infectious disease treatments by targeting peptides presented by MHC molecules. See enclosed Receptor Logic Product Information and information from the Receptor Logic website. The Receptor Logic approach involves the generation of a T-cell receptor mimic antibody (TCRm) that recognizes peptides bound to HLA molecules. In particular, a TCRm (the 4F7 antibody) was generated that recognizes a peptide derived from the host cell protein eIF4G when it is in association with HLA-A2 molecules. eIF4G is a host cell gene product induced by HIV infection and has been identified as a potential CTL vaccine target. The Receptor Logic literature shows that T cells expressing HLA-A2 and infected with HIV could be specifically stained with the 4F7 antibody. The results indicate that the 4F7 antibody successfully detected the eIF4G peptide on the surface of the HIV-infected cells.

Importantly, these results validate Receptor Logic's discovery approach and demonstrate the therapeutic potential of TCRm for anti-infectious disease treatment. According to Receptor Logic, this approach can be used to select optimal vaccine candidates and to monitor the efficacy of such candidates at stimulating the body's immune system. Given the successful results with the 4F7 antibody, it is reasonable to

conclude that the gene products identified by the claimed method would also be useful as vaccines against an infectious disease.

The Veronese reference and the Hunt Declaration

Applicant submits that the previously submitted Veronese reference and Hunt declaration provide sufficient support to enable to the identification of host products as vaccine targets. Veronese teaches that HIV infection upregulates the synthesis of the endogenous host protein, vinculin, which in turn causes the "priming of autoreactive vinculin-specific CTL responses." *See Veronese at page 2515.* The point of the reference was "[t]he identification of naturally processed, class I-presented peptides unique to HIV-infected cells," whether these peptides are viral or endogenous. *See Veronese at page 2509.* Hence, this reference confirms the plausibility of potential vaccine targets for infectious diseases which are based on differentially expressed self-peptides.

As disclosed in the present specification, cellular peptides derived by degradation of endogenously synthesized proteins bind to class I MHC molecules for transport to the cell surface. These class I MHC:peptide complexes are the target antigens for specific CD8⁺ cytotoxic T cells. *See specification at page 14, lines 8-11.* Hence, in order for the peptides to be recognized by the cytotoxic T-cells, the peptides must be presented on the MHC molecule and not as secreted proteins. Therefore, the claims are commensurate in scope with the Declaration of Dr. Donald F. Hunt ("the Hunt Declaration") and one of ordinary skill in the art would be capable of making and using the invention.

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Summary

Given the present amendments, the Veronese reference, the Hunt Declaration, and the newly submitted evidence of Receptor Logic's TCRm, one of ordinary skill in the art would be able to make and use the invention as claimed. Thus, the Applicant believes that the present claims are fully enabled and meet all the requirements of 35 U.S.C. § 112, first paragraph. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicant believes that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Helene C. Carlson
Agent for Applicant
Registration No. 47,473

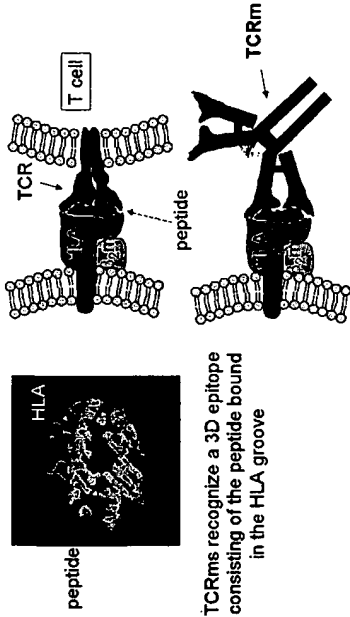
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“GENERATE ANTIBODIES

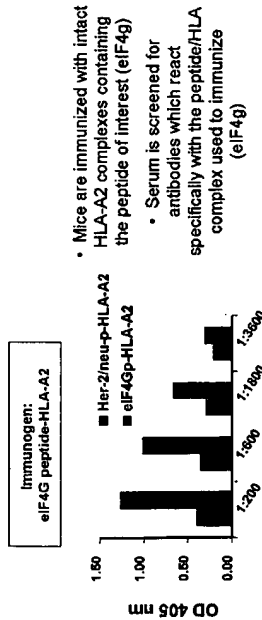
TCR-Mimic Antibodies (TCRm) Recognize Peptides in the Context of HLA Molecules



TCRms recognize a 3D epitope consisting of the peptide bound in the HLA groove

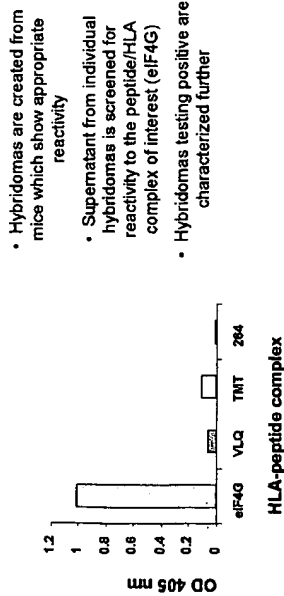
THAT ARE SPECIFIC

Generation of Polyclonal Antibodies Reactive to Specific Peptide-HLA-A2



- Mice are immunized with intact HLA-A2 complexes containing the peptide of interest (eIF4G)
- Serum is screened for antibodies which react specifically with the peptide/HLA complex used to immunize (eIF4G)

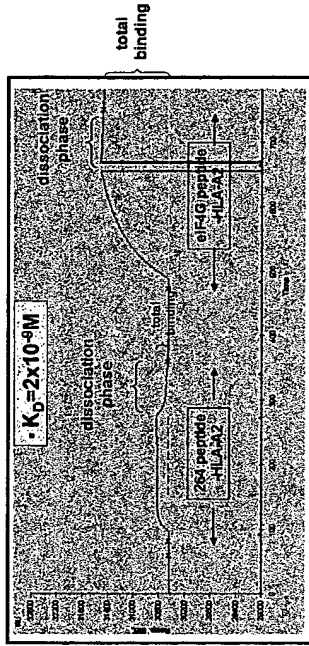
Characterization of 4F7 mAb by ELISA



- Hybridomas are created from mice which show appropriate reactivity
- Supernatant from individual hybridomas is screened for reactivity to the peptide/HLA complex of interest (eIF4G)
- Hybridomas testing positive are characterized further

THAT HAVE HIGH AFFINITIES

TCRm 4F7: Binding Affinity and Specificity Evaluated by BIAcore

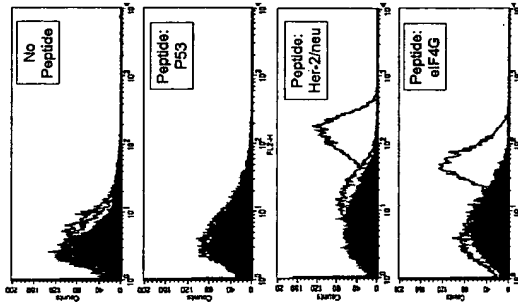


Evaluation of TCRm hybridoma 4F7 by surface plasmon resonance reveals specific binding and high affinity interaction for HLA-A2 loaded with eIF4G peptide

The K_D value for the 4F7 mAb was determined by BIAcore analysis to be 2×10^{-9} M indicating that it is a high affinity antibody.

THAT STAIN PULSED CELLS

Peptide Pulsed T2 Cells Stain with 1B8 or 4F7 TCR mimics



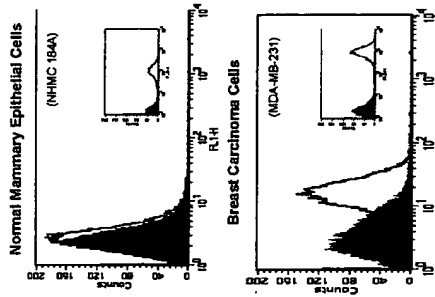
Legend:
— TCRm = 4F7
— TCRm = 1B8
— Isotype control Ab

- T2 cells (HLA-A2⁺, Tap⁺) do not display endogenously processed peptides
- **1B8 is a TCRm with specificity for a peptide from Her-2 in HLA-A2
- Both 4F7 and 1B8 TCRms specifically recognize T2s pulsed with the appropriate peptide and do not cross-react

T2 cells were pulsed for 5 hours with either eIF4G peptide, or a peptide from Her-2, or a peptide from p53 tumor suppressor protein (irrelevant peptide). We show equivalent loading of both peptides based on staining with 8B7.2 mAb which recognizes only conformationally correct HLA-A2 molecules. Flow cytometric results demonstrate that the 4F7 mAb has a greater than 10-fold shift in staining intensity of T2 cells loaded with eIF4G peptide compared to either irrelevant peptide or T2 cells without peptide added. This finding and our ELISA data indicate that the 4F7 mAb is highly specific for the eIF4G peptide in the context of HLA-A2 complex.

AND TUMOR CELLS

TCR-Mimic Antibody (TCRm) 4F7 Blinds Human Breast Cancer Cells

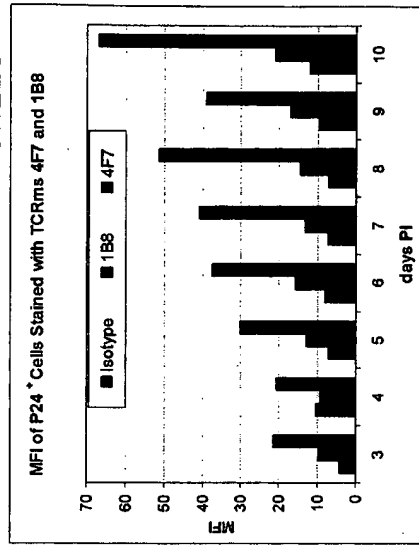


- 4F7 binding indicates eIF4G peptide-HLA-A2 is a novel epitope on a HLA-A2⁺ breast CA cell line
- the eIF4G peptide represents a potential CTL vaccine target

Legend:
— Isotype control
— 4F7 (anti-eIF4G/A2)
— 8B7.2 (anti-HLA-A2)

In order to validate the sensitivity and utility of the 4F7 TCRm we stained the breast cancer cell line (MDA-MB-231) and a cell line representative of normal mammary epithelial tissue. 4F7 stained only the tumor line. The antibody does not stain HLA-A2- cells. Studies are in progress to determine the magnitude of increase of eIF4G peptide-HLA-A2 complexes on the surface of cancerous cells.

AND VIRUS INFECTED CELLS”

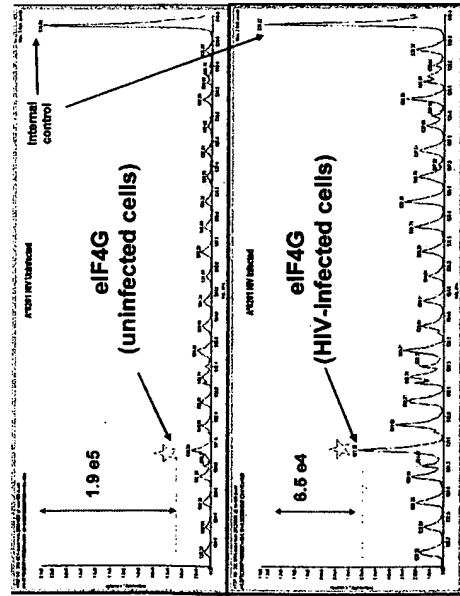
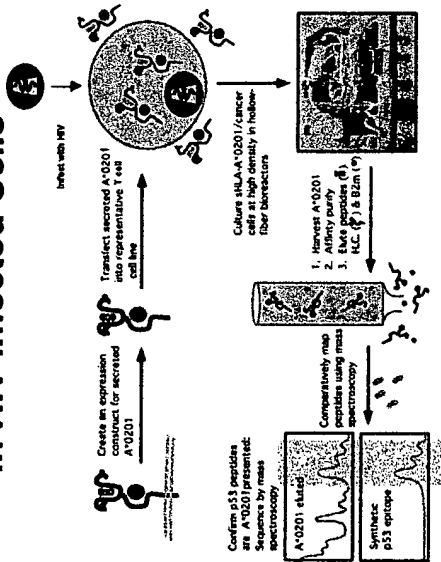


HLA-A2⁺ T cells collected from a healthy donor were infected with HIV and 4F7 antibody detected the presence of the eIF4G peptide on the surface of the cells which also expressed the early HIV antigen P24. This finding validates our discovery process and demonstrates the potential of the TCR mimics. This breakthrough technology is now being applied to the direct discovery, characterization, and targeting of additional antigens unique to the surface of tumor cells.



Pure Protein, L.L.C.

Epitope Discovery: Elevated eIF4G Peptide Presentation in HIV infected Cells



Epitope
Discovery

Pure Protein, L.L.C.

Monoclonal
Antibodies

RECEPTOR
L
G
I
C

Aiming

Selenium, Ltd.



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Turning Knowledge Into Opportunity

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Infected?
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Receptor Logic has developed an integrated diagnostic and therapeutic approach to be used in the design of customized anti-cancer and infectious disease treatments for individual patients. This innovation in antibody discovery and development virtually turns cells inside out by targeting a peptide presented by the ubiquitous MHC molecules on almost all cells. These molecules transport peptides produced in each cell to the surface of that cell to be displayed to the immune system's T-cells. The company is able to generate antibodies against intracellular peptides in the context of MHC molecules. MHC-based genomics and proteomics discoveries focusing on cancer and infectious diseases can now be very valuable when coupled with this technology.

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Technology

- Receptor Logic has a system to design antibodies which can recognize fragments from proteins inside the cell that traditional antibodies cannot see.
- Receptor Logic can select optimal vaccine candidates and monitor their efficacy at stimulating the body's immune system.
- Receptor Logic antibodies are target specific and thus minimize side effects.

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